Research Paper

Brain Atrophy and Physical and Cognitive Disability in Multiple Sclerosis

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ABSTRACT

Introduction: Brain atrophy is associated with physical disability in multiple sclerosis (MS), but there is a great variability between different studies and methodologies, and its use is still limited to research projects. We aimed to analyze the relationship between several volumetric measurements and physical disability and cognitive functioning in MS patients in a clinical practice setting.

Methods: This is a cross-sectional study. A total of 41 patients (31 relapsing-remitting MS, 6 secondary-progressive MS, and 4 primary-progressive MS) were included. Whole brain volume (WBV), gray matter volume (GMV), and T2 lesion load (T2L) were obtained using Icometrix® software. Physical disability was measured with the Expanded Disability Status Scale (EDSS), and cognitive status was evaluated with the brief repeatable battery of neuropsychological tests (BRB-N). The relationship between brain volumes and EDSS was analyzed through linear multivariate regression. The association between volumetry measurements and the number of affected cognitive domains was studied with negative binomial regression.

Results: GMV was associated with age (b=-1.7, P=0.014) and with EDSS (b=-7.55, P=0.013). T2L was associated with EDSS (b=2.29, P=0.032). The number of affected cognitive domains was associated with clinical phenotype, worse in primary progressive MS (PPMS). There was not correlations between cognitive impairment and cerebral volumes.

Conclusion: Brain atrophy measurement is feasible in clinical practice setting, and it is helpful in monitoring the EDSS progression. Primary progressive phenotype is associated with greater risk of cognitive dysfunction.

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Highlights

- The T2 lesion load is associated with physical disability in patients with multiple sclerosis (MS).
- The gray matter volume is associated with age and physical disability in patients with MS.
- There is no significant correlation between cognitive impairment and cerebral volumes in patients with MS.

Plain Language Summary

Conventional magnetic resonance imaging (MRI) is still used for diagnosing and monitoring multiple sclerosis (MS). Analysis of Brain volumes including Whole brain volume (WBV), gray matter volume (GMV), and T2 lesion load (T2L) allows the evaluation of its neurodegenerative mechanisms. Robust evidence links brain atrophy with disability in MS. This study aims to analyze the relationship between advanced MRI sequences and physical disability and cognitive functioning in MS patients. According to the results, T2L was associated with physical disability and GMV was associated with age and physical disability. There was no significant correlation between cognitive impairment and cerebral volumes in patients with MS.

1. Introduction

Conventional MRI sequences continue to be the mainstay in the diagnosis and monitoring of multiple sclerosis (MS) patients. However, they mainly assess the inflammatory processes of MS and therefore its correlation with clinical outcomes is only partial (Filipp & Grossman, 2002; Li et al., 2006; Fisniku et al., 2008; Enzinger et al., 2001; Rudick et al., 2006; Minneboo et al., 2009). Brain volumes analysis allow the evaluation of its neurodegenerative mechanisms. There is a robust evidence linking brain atrophy with disability in MS (Kearney et al., 2014; Popescu et al., 2013; Pérez-Miralles et al.,2015; Deloire et al., 2011; Benedict et al., 2013; Calabrese et al., 2011; Azevedo et al., 2015; Rocca et al., 2017; Vollmer et al., 2016; Vidal-Jordana et al., 2018), and the incorporation of these techniques into the routine daily basis could be of great value to improve the follow-up of this disease. Nonetheless there are still many methodological and biological factors that generate an important variability in their results, and hold back its use to research projects (Sastre-Garriga et al., 2017). The objective of this study is to analyze the relationship between advanced MRI sequences and physical disability and cognitive functioning in MS patients in a clinical practice setting in order to increase our knowledge of these techniques and move forward its implementation as another routine evaluation tool.

2. Materials and Methods

This research is a cross-sectional study. We included MS patients according the McDonald 2010 criteria (Polman et al., 2011) attending the demyelinating diseases unit at Torrejon University Hospital, Madrid, between December/2015 and December/2016. The patients gave their informed consent. The study complied with the Helsinki declaration and the results are completely confidential according to the personal data protection law (1999).

Clinical and epidemiological data were obtained retrospectively through review of the medical charts. Cognitive functioning was evaluated with the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (Rao et al., 1991), which consists of the Selective Reminding Test (verbal memory), the Paced Auditory Serial Adittion Test (PASAT) (working memory), verbal fluency test and Symbol Digit Modalities Test (SDMT) (executive functions and speed processing) and Spatial Recall Test (SPART) (visual memory). The results were adjusted to age, sex and education level for the Spanish population (Duque et al., 2012). We also obtained the Beck Depression Inventory-II (BDI-II) (Sacco et al., 2016)and the Multiple Sclerosis Fatigue Scale (Fisk et al., 1994; Casanova et al., 2000). Advanced MRI evaluation was done by Icometrix® software through T1-3D and FLAIR-3D sequences. We analyzed whole brain volume (WBV), Gray Matter Volume (GMV) and T2 lesion load (T2). We defined cognitive dysfunction for a cognitive domain as a score lower than 1.5 standard deviations in its neuropsychological test. The association between brain volume measurements and clinical variables was studied with lineal multivariate regression, and between brain volumetry and number of affected cognitive domains with negative binomial regression. Statistical analysis was done with SPSS software, version 19. Statistical significance was set at P<0.05.

3. Results

A total of 41 patients were studied, including 31 relapsing-remitting MS (RRMS), 6 secondary progressive MS (SPMS), and 4 primary progressive MS (PPMS). 27 samples were women. Mean age was 43.85±11.1 years, and mean duration of MS was 8±1.09 years. Mean score of EDSS was 2.6±1.9 and median EDSS 2 (Intercuartile range (IQR): 1.0-4.0). Average education level was 11.5±3.3 years. Mean score of BDI-II was 12.2±9.0, and mean score of MSFS was 9.4±8.9 (Table 1).

Average number of affected cognitive domains was 0.83±6.3. 25 patients (61%) obtained normal punctuations in all the tests. 7 patients had impairment in 1 cognitive domain, and 9 patients (22%) had two or more (Table 2). The most frequent affected cognitive domain was working memory (29.3%), followed by speed processing (17.1%) and verbal memory (12.2%) (Table 3).

Multivariate regression analysis found a relationship between WBV and age (b= -2.4, P=0.037), GMV with age (b=-1.7, P=0.014) and EDSS (b=-7.55; P=0.013), and finally T2L with EDSS (b=2.29; P=0.032).

Negative binomial regression analysis revealed an association between cognitive dysfunction and clinical phenotype (greater dysfunction in PPMS) (OR RRMS/PPMS 0.037, P=0.016; OR SPMS/PPMS 0.02, P=0.028), but not with MRI data (WBV P=0.383; GMV P=0.495; T2L p=0.451).

4. Discussion

In our study we obtained a proportion of cognitive dysfunction (impairment in 2 or more cognitive domains) of 22%, lower than other published series, normally ranging 40-60%. This difference could be explained to the composition of our sample with a predominance of RRMS, which is associated with a lesser cognitive damage (Chiaravalloti & DeLuca, 2008; Denney et al., 2005; Ruano et al., 2017), and low disability (global mean EDSS: 2.6, and mean EDSS in the RRMS group of 1.8). Nonetheless, cognitive impairment can be present even in early phases of the disease, and in patients with a good clinical situation (Migliore et al., 2017; Amato et al., 2001; Hankomäki et al., 2014), so the differences between different samples must be related to other factors not completely understood.

Regarding the affected cognitive domains we obtained similar results to other studies, with more repercussion in executive functions, speed processing and verbal memory (Rao, 1995; Benedict et al., 2002), although we also got a lower percentage of dysfunction of these domains compared to other studies.

When we analyzed the relationship between volumetry measurements and cognitive status we only obtained an association with the clinical phenotype. This result is in line with previous works, in which cognitive dysfunction is more frequent and more intense among progressive forms of the disease (Chiaravalloti & DeLuca, 2008; Denney et al., 2005; Ruano et al., 2017). In our study it is noteworthy the lack of association between cognitive impairment and advanced MRI sequences (WBV and GMV). In spite of the differences in the methodologies of different studies, most of them find correlations between brain volumes

Table 1. Clinical and demographic characteristics of our sample

MS Phenotype	N (M/F)	Mean±SD		Mean±SD	Median (IQR)	Mean±SD		
	Sex	Age (y)	DD (y)	EDSS		Ed. Level (y)	BDI-II	MSFS
Total	27/14	43.9±11.1	8.0±1.09	2.6±1.9	2(1-4)	11.5±3.3	12.2±9.0	9.4±8.9
RRMS (n=31)	22/9	41.9±11.0	11.2±10.7	1.8±1.2	2(1-3)	11.9±3.5	12.0±9.9	6.6±7.3
SPMS (n=6)	3/3	47.8±9.6	22.5±7.9	5.2±1.7	5(3.5-7)	9.7±2.3	12.8±5.3	22.0±4.7
PPMS (n=4)	2/2	53.3±9.8	3.5±2.1	4.5±2.3	4(4-6.5)	11.3±2.9	13±7.0	10.0±4.0

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N: Number of patients; RRMS: Relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary-progressive multiple sclerosis; M/F: male/female; DD: Duration of the disease; EDSS: Expanded Disability Status Scale; Ed. Level: education level (years); BDI-II: Beck Depression Inventory-II; MSFS: Multiple Sclerosis Fatigue Scale

Table 2. Number of affected cognitive domains

Affected Cognitive Domains	0	1	2	3	4	5
No. (%)	25(61)	7(17)	3(7)	3(7)	3(7)	0(0)

N: number of patients

Table 3. Results of Brief Repeatable Battery of Neuropsychological Tests (BRB-N)

Result	No. (%)								
	Verbal Memory		Visual Memory		Working Memory		Speed Processing		Fluency
Normal	SRT-S SRT-R SRT-D	37(90.2) 36(87.8) 38(92.7)	SPART-Total	41(100)	PASAT	29(70.7)	SDMT	34(82.9)	38(92.7)
Impaired	SRT-S SRT-R SRT-D	4(9.8) 5(12.2) 3(7.3)	SPART-D	0(0)	PASAT	12(29.3)	SDMT	7(17.1)	3(7.3)

SRT-S: Selective reminding test-Storage; SRT-R: Selective reminding test-Retrieval; SRT-D: Selective reminding test-Delayed; SPART: Spatial recall test-Total; SPART-D: Spatial recall test-Delayed; PASAT: Paced auditory serial addition test; SDMT: Symbol digit modalities test

and physical and cognitive functioning (Rocca et al., 2017; Vollmer et al., 2016). In our study is especially striking for the GMV which is one of the brain volume measurements with a greater impact in the disability in MS (Steenwijk et al., 2016; Filippi et al., 2013; Fisher et al., 2008; Rudick et al., 2009). Again, these differences could be justified by methodological reasons, regarding the design of the study (cross-sectional instead of longitudinal), the characteristics of our sample (low frequency of cognitive impairment), as well as technical factors related to the acquisition and analysis of the images (Eshaghi et al., 2018).

Multivariate regression showed a significant relationship between EDSS and GMV and T2L. In this regard there is also a great variability among different studies, but most of them find a positive association between these data, especially with the atrophy of the gray matter (Eshaghi et al., 2018), and even with composite measurements of GMV-T2L (Moodie et al., 2012; Gauthier et al., 2007). At last, we also found a correlation between age and a loss of cerebral volume, both global and gray matter. This result could be expected as brain volume decrease physiologically with age and with a longer duration of the disease.

5. Conclusion

we can say that our study corroborates that brain atrophy measurements can be incorporated into the daily basis evaluation of MS patients. Specifically T2 load and Gray Matter volume are helpful in monitoring the EDSS progression. On the other hand, we also add evidence to the importance of the cognitive impairment and volumetric changes occurring in MS, as well as the differences between the different clinical forms of the disease (greater cognitive impairment in progressive MS). Finally some results, in particular the lack of association between volumetry data and cognitive dysfunction, show the importance of continuing the research of the neurodegenerative processes of MS.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished, and if desired, the research results would be available to them. A written consent has been obtained from the subjects. principles of the Helsinki Convention was also observed.

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Authors' contributions

Conceptualización, Methodology, Formal Analysis, Data Curation, Writing Original, Draft Preparation: Luis Ignacio Casanova Peño; Conceptualización, Methodology, Formal Analysis, Data Curation, Writing Original, Draft Preparation, Supervision, Project Administration, Funding Acquisition: Carlos López De Silanes De Miguel; Conceptualización, Methodology, Formal Analysis, Data Curation, Writing Original, Draft Preparation: Laura de Torres; Writing-review & editing, visualization: Miriam Eimil Ortiz, María José Gil Moreno, Beatriz Oyanguren Rodeño, Rodrigo Terrero Carpio, Blanca Patricia Díaz Montoya, Julia Sabín Muñoz, Julia Sabín Muñoz, Miguel Ángel Saiz Sepúlveda and Marta González Salaices; Software, Resources, Writing-review & editing: Esther De Antonio Sanz; Resources, writing-review & editing: Sara Abellán Ayuso.

Conflict of interest

The authors declared no conflict of interest.

References

Filippi, M., & Grossman, R. I. (2002). MRI techniques to monitor MS evolution: The present and the future. *Neurology, 58*(8), 1147-1153. [DOI:10.1212/WNL.58.8.1147] [PMID]

Li, D. K., Held, U., Petkau, J., Daumer, M., Barkhof, F., & Fazekas, F., et al. (2006). MRI T2 lesion burden in multiple sclerosis: A plateauing relationship with clinical disability. *Neurology, 66*(9), 1384-1389. [DOI:10.1212/01.wnl.0000210506.00078.5c] [PMID]

Fisniku, L. K., Brex, P. A., Altmann, D. R., Miszkiel, K. A., Benton, C. E., & Lanyon, R., et al. (2008). Disability and T2 MRI lesions: A 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain : A Journal of Neurology, 131*(Pt 3), 808-817. [DOI:10.1093/brain/awm329] [PMID]

Enzinger, C., Fuchs, S., Pichler, A., Wallner-Blazek, M., Khalil, M., & Langkammer, C., et al. (201). Predicting the severity of relapsing-remitting MS: the contribution of cross-sectional and short-term follow-up MRI data. *Multiple Sclerosis (Houndmills, Basingstoke, England), 17*(6), 695-701. [DOI:10.1177/1352458510394454] [PMID]

Rudick, R. A., Lee, J. C., Simon, J., & Fisher, E. (2006). Significance of T2 lesions in multiple sclerosis: A 13-year longitudinal study. *Annals of Neurology, 60*(2), 236-242. [DOI:10.1002/ana.20883] [PMID]

Minneboo, A., Uitdehaag, B. M., Jongen, P., Vrenken, H., Knol, D. l., & van Walderveen, M. A., et al. (2009). Association between MRI parameters and the MS severity scale: A 12 year follow-up study. *Multiple Sclerosis (Houndmills, Basingstoke, England), 15*(5), 632-637. [DOI:10.1177/1352458509102617] [PMID]

Kearney, H., Rocca, M. A., Valsasina, P., Balk, L., Sastre-Garriga, J., & Reinhardt, J., et al. (2014). Magnetic resonance imaging correlates of physical disability in relapse onset multiple sclerosis of long disease duration. *Multiple Sclerosis (Houndmills, Basingstoke, England), 20*(1), 72-80. [DOI:10.1177/1352458513492245] [PMID] [PMCID]

Popescu, V., Agosta, F., Hulst, H. E., Sluimer, I. C., Knol, D. L., & Sormani, M. P., et al. (2013). Brain atrophy and lesion load predict long term disability in multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry, 84*(10), 1082-1091 [DOI:10.1136/jnnp-2012-304094] [PMID]

Pérez-Miralles, F. C., Sastre-Garriga, J., Vidal-Jordana, A., Río, J., Auger, C., & Pareto, D., et al. (2015). Predictive value of early brain atrophy on response in patients treated with interferon β. *Neurology(R) Neuroimmunology & Neuroinflammation, 2*(4), e132. [DOI:10.1212/NXI.0000000000000132] [PMID] [PMCID]

Deloire, M. S., Ruet, A., Hamel, D., Bonnet, M., Dousset, V., & Brochet, B. (2011). MRI predictors of cognitive outcome in early multiple sclerosis. *Neurology, 76*(13), 1161-1167. [DOI:10.1212/WNL.0b013e318212a8be] [PMID] [PMCID]

Benedict, R. H., Hulst, H. E., Bergsland, N., Schoonheim, M. M., Dwyer, M. G., & Weinstock-Guttman, B., et al. (2013). Clinical significance of atrophy and white matter mean diffusivity within the thalamus of multiple sclerosis patients. *Multiple Sclerosis (Houndmills, Basingstoke, England), 19*(11), 1478-1484. [DOI:10.1177/1352458513478675] [PMID]

Calabrese, M., Rinaldi, F., Grossi, P., & Gallo, P. (2011). Cortical pathology and cognitive impairment in multiple sclerosis. *Expert Review of Neurotherapeutics, 11*(3), 425-432. [DOI:10.1586/ern.10.155] [PMID]

Azevedo, C. J., Overton, E., Khadka, S., Buckley, J., Liu, S., & Sampat, M., et al. (2015). Early CNS neurodegeneration in radiologically isolated syndrome. *Neurology(R) Neuroimmunology & Neuroinflammation, 2*(3), e102. [DOI:10.1212/NXI.0000000000000102] [PMID] [PMCID]

Rocca, M. A., Comi, G., & Filippi, M. (2017). The role of T1-Weighted derived measures of neurodegeneration for assessing disability progression in multiple sclerosis. *Frontiers in Neurology, 8*, 433. [DOI:10.3389/fneur.2017.00433] [PMID] [PMCID]

Vollmer, T., Huynh, L., Kelley, C., Galebach, P., Signorovitch, J., & DiBernardo, A., et al. (2016). Relationship between brain volume loss and cognitive outcomes among patients with multiple sclerosis: A systematic literature review. *Neurological Sciences, 37*(2), 165-179. [DOI:10.1007/s10072-015-2400-1] [PMID]

Vidal-Jordana, A., Sastre-Garriga, J., Pareto, D., Tur, C., Arrambide, G., & Otero-Romero, S., et al. (2018). Brain atrophy 15 years after CIS: Baseline and follow-up clinico-radiological correlations. *Multiple Sclerosis (Houndmills, Basingstoke, England), 24*(6), 721-727. [DOI:10.1177/1352458517707070] [PMID]

Sastre-Garriga, J., Pareto, D., & Rovira, À. (2017). Brain atrophy in multiple sclerosis: Clinical relevance and technical aspects. *Neuroimaging Clinics of North America, 27*(2), 289-300. [DOI:10.1016/j.nic.2017.01.002] [PMID]

Polman, C. H., Reingold, S. C., Banwell, B., Clanet, M., Cohen, J. A., & Filippi, M., et al. (2011). Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals of Neurology, 69*(2), 292-302. [DOI:10.1002/ana.22366] [PMID] [PMCID]

Rao, S. M., Leo, G. J., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology, 41*(5), 685-691. [DOI:10.1212/WNL.41.5.685] [PMID]

Duque, P., Ibanez, J., Del Barco, A., Sepulcre, J., de Ramon, E., & Fernandez-Fernandez, O., et al. (2012). [Normalisation and validation of the Brief Neuropsychological Battery as the reference neuropsychological test in multiple sclerosis (Spanish)]. *Revista de Neurologia, 54*(5), 263-270. [DOI:10.33588/rn.5405.2011452]

Sacco, R., Santangelo, G., Stamenova, S., Bisecco, A., Bonavita, S., & Lavorgna, L., et al. (2016). Psychometric properties and validity of Beck depression inventory II in multiple sclerosis. *European Journal of Neurology, 23*(4), 744-750. [DOI:10.1111/ene.12932] [PMID]

Fisk, J. D., Pontefract, A., Ritvo, P. G., Archibald, C. J., & Murray, T. J. (1994). The impact of fatigue on patients with multiple sclerosis. *The Canadian Journal of Neurological Sciences, 21*(1), 9-14. [DOI:10.1017/S0317167100048691]

Casanova, B., Coret, F., & Landete, L. (2000). [A study of various scales of fatigue and impact on the quality of life among patients with multiple sclerosis (Spanish)]. *Revista de Neurologia, 30*(12), 1235-1241. [DOI:10.33588/rn.3012.99436]

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *The Lancet. Neurology, 7*(12), 1139-1151. [DOI:10.1016/S1474-4422(08)70259-X] [PMID]

Denney, D. R., Sworowski, L. A., & Lynch, S. G. (2005). Cognitive impairment in three subtypes of multiple sclerosis. *Archives of Clinical Neuropsychology, 20*(8), 967-981 [DOI:10.1016/j.acn.2005.04.012] [PMID]

Ruano, L., Portaccio, E., Goretti, B., Niccolai, C., Severo, M., & Patti, F., et al. (2017). Age and disability drive cognitive impairment in multiple sclerosis across disease subtypes. *Multiple Sclerosis (Houndmills, Basingstoke, England), 23*(9), 1258-1267. [DOI:10.1177/1352458516674367] [PMID]

Migliore, S., Ghazaryan, A., Simonelli, I., Pasqualetti, P., Squitieri, F., & Curcio, G., et al. (2017). Cognitive Impairment in relapsing-remitting multiple sclerosis patients with very mild clinical disability. *Behavioural Neurology, 2017*, 7404289. [DOI:10.1155/2017/7404289] [PMID] [PMCID]

Amato, M. P., Ponziani, G., Siracusa, G., & Sorbi, S. (2001). Cognitive dysfunction in early-onset multiple sclerosis: A reappraisal after 10 years. *Archives of Neurology, 58*(10), 1602-1606. [DOI:10.1001/archneur.58.10.1602] [PMID]

Hankomäki, E., Multanen, J., Kinnunen, E., & Hämäläinen, P. (2014). The progress of cognitive decline in newly diagnosed MS patients. *Acta Neurologica Scandinavica, 129*(3), 184-191. [DOI:10.1111/ane.12161] [PMID]

Rao S. M. (1995). Neuropsychology of multiple sclerosis. *Current Opinion in Neurology, 8*(3), 216-220. [DOI:10.1097/00019052-199506000-00010] [PMID]

Benedict, R. H., Fischer, J. S., Archibald, C. J., Arnett, P. A., Beatty, W. W., & Bobholz, J., et al. (2002). Minimal neuropsychological assessment of MS patients: A consensus approach. *The Clinical Neuropsychologist, 16*(3), 381-397. [DOI:10.1076/clin.16.3.381.13859] [PMID]

Steenwijk, M. D., Geurts, J. J., Daams, M., Tijms, B. M., Wink, A. M., & Balk, L. J., et al. (2016). Cortical atrophy patterns in multiple sclerosis are non-random and clinically relevant. *Brain, 139*(Pt 1), 115-126. [DOI:10.1093/brain/awv337] [PMID]

Filippi, M., Preziosa, P., Copetti, M., Riccitelli, G., Horsfield, M. A., & Martinelli, V., et al. (2013). Gray matter damage predicts the accumulation of disability 13 years later in MS. *Neurology, 81*(20), 1759-1767. [DOI:10.1212/01.wnl.0000435551.90824.d0] [PMID]

Fisher, E., Lee, J. C., Nakamura, K., & Rudick, R. A. (2008). Gray matter atrophy in multiple sclerosis: A longitudinal study. *Annals of Neurology, 64*(3), 255-265. [DOI:10.1002/ana.21436] [PMID]

Rudick, R. A., Lee, J. C., Nakamura, K., & Fisher, E. (2009). Gray matter atrophy correlates with MS disability progression measured with MSFC but not EDSS. *Journal of The Neurological Sciences, 282*(1-2), 106-111. [DOI:10.1016/j.jns.2008.11.018] [PMID] [PMCID]

Eshaghi, A., Prados, F., Brownlee, W. J., Altmann, D. R., Tur, C., & Cardoso, M. J., et al.(2018). Deep gray matter volume loss drives disability worsening in multiple sclerosis. *Annals of Neurology, 83*(2), 210-222. [DOI:10.1002/ana.25145] [PMID] [PMCID]

Moodie, J., Healy, B. C., Buckle, G. J., Gauthier, S. A., Glanz, B. I., & Arora, A., et al. (2012). Magnetic Resonance Disease Severity Scale (MRDSS) for patients with multiple sclerosis: A longitudinal study. *Journal of The Neurological Sciences, 315*(1-2), 49-54. [DOI:10.1016/j.jns.2011.11.040] [PMID] [PMCID]

Gauthier, S. A., Mandel, M., Guttmann, C. R., Glanz, B. I., Khoury, S. J., & Betensky, R. A., et al. (2007). Predicting short-term disability in multiple sclerosis. *Neurology, 68*(24), 2059-2065. [DOI:10.1212/01.wnl.0000264890.97479.b1] [PMID]